## REMARKS

By this amendment, claim 1 is amended and claim 14 is canceled without prejudice or disclaimer. These amendments are made to even more clearly recite the claimed invention, do not add prohibited new matter and are fully supported by the specification. Reconsideration and withdrawal of the rejections in the outstanding Office Action are respectfully requested in view of the foregoing amendments and the following remarks.

Claim Rejections – 35 U.S.C. § 102

The Office Action rejects claims 1, 6, 7, and 11 under 35 U.S.C. 102(b) as being anticipated by Wang et al. (J. Med. Chem., Vol. 37, pp. 4479-4489 (1994), hereinafter "WANG"). In response, Applicants respectfully maintain that WANG does not anticipate the claimed invention.

Initially, while Applicants had previously argued this point to the Office and explained how Applicants' invention estimates the binding scheme of the lead candidate compounds to the structure of the protein, the Office apparently remains unconvinced. Thus, in an effort to make clearer this aspect of the invention, Applicants have amended claim 1 to recite that the claimed method uses the three-dimensional structure of the protein. Applicants respectfully submit that this aspect of the invention is advantageous in that it allows for greater certainty in the choice of lead compounds, as it is based on the real three-dimensional structure of the protein. Applicants maintain that WANG fails to show at least this aspect of the invention.

As previously explained, WANG is directed to a method for finding compounds that bind to protein kinase C (PK-C). WANG relies on information of the pharmacophore of PDBU (phorbol 12, 13-dibutyrate), which is known to bind to PK-C ("protein kinase C") (*see* page 4480, col. 1,

paragraph 2, of WANG). Based on the crystal structure of the phorbol ester and information on binding sites of PDBU, WANG constructed a 3D pharmacophore query for PDBU (*see* page 4480, col. 1, paragraph 3, of WANG). This pharmacophore query did not include information on the binding sites or three-dimensional structure of the PK-C protein; the search relied solely on information on the pharmacophore structure of PDBU. Indeed, WANG acknowledges that "the 3D structure of the PK-C receptor has not yet been determined" (*see* page 4480, col. 1, paragraph 2, of WANG).

In responding to Applicant's arguments, the Office Action makes the following assertions about WANG's disclosure.

> Wang et al. further teaches the determination that conformational changes of ligands upon binding [to] protein receptors do not have to be in their local energy minima to bind (see Wang et al., page 4485, col. 1, line 30 through 4886, col. 1, line 9). Contrary to [Applicant's] argument, the determination of the effects [of] conformation changes in modeled ligand structures following receptor binding, as taught by Wang et al., reads directly on estimating a binding scheme of lead-candidate compounds to a protein as instantly claimed. Further, the disclosed modeling of ligand conformations upon protein binding by Wang et al. reads directly on a correspondence of the mode of covalent bonds of partial structures of query and [trial] compounds as instantly claimed.

(Office Action, page 5, last full paragraph, to page 6.) Applicant respectfully submits that the Office Action appears to misinterpret WANG.

The first paragraph of the cited passage from WANG (page 4485, col. 1, line 30 through 4886, col. 1, line 9), which begins "4. Conformational Energy," discusses energy costs to fit compounds to the pharmacophore. This paragraph states that, "Our recent studies [citations omitted] on the conformational changes of ligands upon binding on protein receptors have shown that ligands to not have to be in their global or local energy minima to bind and that the deformation of a ligand

upon binding to a receptor is a common phenomenon." (Lines 15-20 of cited paragraph.) Clearly, WANG is referring to previous studies, not the present WANG article, which is cited as a reference by the Office. Thus, contrary to the Office's position, WANG does not teach "the determination that conformational changes of ligands upon binding on protein receptors do not have to be in their local energy minima to bind" – that teaching is apparently disclosed in other publications. To the extent that the Office's conclusion of anticipation relies upon this passage, its conclusion appears to be misplaced.

The only sections from the passages cited by the Office that can be said to actually discuss an interaction between a ligand and a protein begin at line 21 of the right column of page 4485. In this section, WANG proposes that the interaction energy between a ligand and a binding site can be estimated by a pair of equations, the values for which are obtained from "[o]ur previous modeling study [citations omitted] on the binding site of PK-C." (Page 4485, right column, lines 39-40.) Applicants respectfully submit that this section does not teach or suggest, "estimating a binding scheme of the lead-candidate compounds to the three-dimensional structure of the protein based on three-dimensional information of the query molecule," and for at least this reason as well, WANG does not anticipate the present invention.

Applicant respectfully submits that for an anticipation rejection to be made, the Office has the burden of showing how every element of Applicants' claim is found within a single teaching. Applicant respectfully submits that the Office has failed to meet its burden in this instance, as WANG fails to disclose – within the four corners of the document – each and every element of

Applicant's claims. For at least the reasons discussed herein, Applicant submits that the claimed invention is not anticipated and request withdrawal of the rejection.

## CONCLUSION

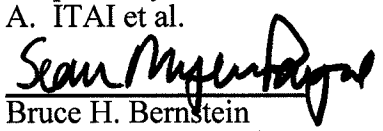
In view of the foregoing, Applicant submits that the Examiner's rejections should be withdrawn. Entry and consideration of the present amendment, reconsideration of the outstanding Office Action, and allowance of the present application and all of the claims therein are respectfully requested and now believed to be appropriate.

Any amendments to the claims which have been made in this amendment, and which have not been specifically noted to overcome a rejection based upon the prior art, should be considered to have been made for a purpose unrelated to patentability, and no estoppel should be deemed to attach thereto.

Should the Commissioner determine that any extension of time is required in order to render this response timely and/or complete, including any extension required for entry of an Examiner's amendment, the Commissioner is authorized to charge such required extension of time fee under 37 C.F.R. §1.17 to Deposit Account No. 19-0089.

If the Examiner has any questions, or wishes to discuss this matter, the Examiner is respectfully requested to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
A. ITAI et al.



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